01-24-07

AF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Curtiss et al.	ART UNIT:	1645
Serial No.:	09/120,970	EXAMINER:	PORTNER, Virginia A.
Filed:	July 22, 1998		
Entitled:	RECOMBINANT BACTERIAL VACCINE SYSTEM WITH ENVIRONMENTALLY LIMITED VIABILITY		

Attorney Docket No.: MEG-207.0 US-1

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Sir:

Transmitted herewith: [X] A corrected Brief on Appeal pursuant to 37 C.F.R. §41.37 (26 pages); and [X] a return-receipt postcard, for filing in the above-captioned patent application.

FEE FOR ADDITIONAL CLAIMS

[X] A fee for additional claims is not required.

[ ] A fee for additional claims is required. The additional fee has been calculated as shown below:

	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	NUMBER OF EXCESS CLAIMS	RATE	FEES DUE
TOTAL CLAIMS	--	--	00	× $25	= 0.00
INDEPENDENT	-	-	0	× $100	= 0.00
FIRST INTRODUCTION OF MULT. DEPENDENT CLAIM				+$180	= 0.00
TOTAL FEES DUE					= **0.00**

PAYMENT OF ADDITIONAL FEES

[ ] A check including the amount of $_____ in payment of the fees for filing a brief in support of an appeal under 37 C.F.R.§41.37 is enclosed.

[X] The Commissioner is hereby authorized to charge payment of any additional fees required under 37 CFR 1.16 or 1.17 in connection with the paper(s) transmitted herewith, or to credit any overpayment of same, to Deposit Account No.50-0268. A duplicate copy of this transmittal letter is submitted herewith.

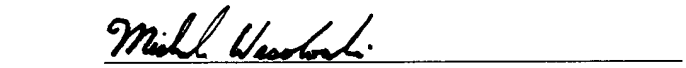
PETITION FOR EXTENSION OF TIME

[ ] Extension is requested under 37 CFR 1.136(a), and the following extension fee is applicable for the Response filed herewith: [ ] $60.00 for response within first month pursuant to 37 CFR 1.17(a)(1);
[ ] $225.00 for response within second month pursuant to 37 CFR 1.17(a)(2);
[ ] $510.00 for response within third month pursuant to 37 CFR 1.17(a)(3);
[ ] $795.00 for response within fourth month pursuant to 37 CFR 1.17(a)(4);
[ ] $1,080.00 for response within fifth month pursuant to 37 CFR 1.17(a)(5).

[ ] A check including the amount of [ ] $60.00 [ ] $225.00 [ ] $510.00 [ ] $795.00 [ ] $1,080.00 in payment of the extension fee is transmitted herewith.

[X] The Commissioner is hereby authorized to charge payment of any additional fees required in connection with the paper(s) transmitted herewith, or to credit any overpayment of same, to Deposit Account No. 50-0268. A duplicate of this transmittal letter is submitted herewith.

Respectfully submitted,



Leon R. Yankwich, Reg. No. 30,237
Michael R. Wesolowski, Reg. No. 50,944
Attorneys for Appellants
Yankwich & Associates, P.C.
201 Broadway
Cambridge, MA 02139
Telephone: (617) 374-3700
Facsimile: (617) 374-0055

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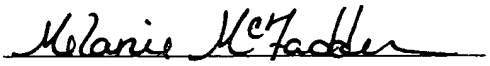

Melanie McFadden

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application of:	Curtiss et al.	ART UNIT:	1645
Serial No.:	09/120,970	EXAMINER:	PORTNER, Virginia A.
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CORRECTED BRIEF ON APPEAL

Sir:

This paper is filed in response to the Notice of non-compliant Appeal Brief dated December 20, 2006 in the above-identified patent application.

On November 14, 2006, Appellants submitted a Brief on Appeal setting forth the basis of their appeal from the Office Action mailed November 8, 2005, which finally rejected Claims 30, 32-39, 41-51, and 53-65 of the above-identified patent application. On December 20, 2006, Appellants received a subsequent Office communication noting that Appellants' Brief on Appeal failed to comply with 37 C.F.R. §41.37(c) because the brief did not contain the items required, specifically, no evidence appendix was included. However, because the defective brief appeared to be a *bona fide* attempt to respond, Applicants were given thirty days to submit a corrected amendment in compliance with 37 C.F.R. §41.37.

Pursuant to 37 CFR §41.37, Appellants submit this corrected Brief on Appeal.

No fees are believed to be due; however, the Commissioner is authorized to charge any additional fees required in connection with the papers filed herewith to Deposit Account No. 50-0268.

TABLE OF CONTENTS

REAL PARTY IN INTEREST

The real parties in interest for the above-captioned patent application are Washington University, whose principal place of business is located at 660 South Euclid Avenue CB 8013, St. Louis, MO 63110-1093 and AVANT Immunotherapeutics, Inc., whose principal place of business is located at 119 Fourth Avenue, Needham, MA 02494-2725, as assignees of an undivided one-half, joint interest in and to the above-identified patent application by virtue of Assignments recorded at Reel 7600, Frame 0008 and Reel 014271, Frame 0664, respectively.

RELATED APPEALS AND INTERFERENCES

Neither Appellants nor their representatives are aware of any other appeals or interferences that would directly affect, be affected by, or have a bearing on the Board's decision in this appeal.

STATUS OF THE CLAIMS

The present status of all claims is shown in the following table, with claims being appealed marked accordingly.

Claim No.	Claim Status	Status on Appeal
1	canceled	
2	canceled	
3	canceled	
4	canceled	
5	canceled	
6	canceled	
7	canceled	
8	canceled	
9	canceled	
10	canceled	
11	canceled	
12	canceled	
13	canceled	
14	canceled	
15	canceled	
16	canceled	

17	canceled	
18	canceled	
19	canceled	
20	canceled	
21	canceled	
22	canceled	
23	canceled	
24	canceled	
25	canceled	
26	canceled	
27	canceled	
28	canceled	
29	canceled	
30	rejected	appealed
31	canceled	
32	rejected	appealed
33	rejected	appealed
34	rejected	appealed
35	rejected / objected to	appealed
36	rejected	appealed
37	rejected	appealed
38	rejected	appealed
39	rejected	appealed
40	canceled	
41	rejected	appealed
42	rejected	appealed
43	rejected	appealed
44	rejected	appealed
45	rejected	appealed
46	rejected	appealed
47	rejected	appealed
48	rejected	appealed
49	rejected	appealed

50	rejected	appealed
51	rejected	appealed
52	canceled	
53	rejected	appealed
54	rejected	appealed
55	rejected	appealed
56	rejected	appealed
57	rejected	appealed
58	rejected	appealed
59	rejected	appealed
60	rejected	appealed
61	rejected	appealed
62	rejected	appealed
63	rejected	appealed
64	rejected	appealed
65	rejected	appealed

STATUS OF AMENDMENTS

The requested amendments of Appellants' submission under 37 CFR §116(b), filed April 10, 2006, were not entered.

SUMMARY OF THE CLAIMED SUBJECT MATTER

The present invention and claims are directed to environmentally limited viability systems (ELVS) for microbes based on differences in environmental conditions, i.e., permissive and non-permissive environments. [Page 5, lines 14-19] Viability of the microorganisms is limited to the permissive environment by specifically expressing one or more essential genes while only in the permissive environment, and, optionally, expressing one or more lethal genes only in the non-permissive environment. [Page 10, lines 1-6] The essential genes are those required for cell viability [Page 11, lines 15-19] and include genes for cell metabolism or growth [page 12, line 26 – page 13, line 6] and genes essential for cell wall or cell membrane integrity [page 13, line 7 – page 16, line 3]. The expression/non-expression of the genes is controlled by regulatory elements that enable the essential genes (and optionally, lethal genes) to be differentially expressed in permissive versus non-permissive

environments such that the cell is viable in the permissive environment and not viable in the non-permissive environment. [Page 18, lines 10-17] The switch in expression is mediated by environmentally based changes in trans-regulatory elements [Page 18, lines 17-27].

GROUNDS OF REJECTION TO BE REVIEWED

The following issues remain after the final rejection:

(1) Whether the present claims, which are directed to environmentally limited viability systems (ELVS) for microbes based on differences in environmental conditions, i.e., permissive and non-permissive environments, are obvious under the judicially created doctrine of obviousness-type double patenting in view of the claims of the later-filed but first to issue US Patent No. 6,780,405, which claims are directed to regulated antigen delivery systems (RADS); and

(2) Whether claims specifying plasmid pMEG-104 recite subject matter which is not described in the specification in such a way as to enable one skilled in the art to make and use the invention.

ARGUMENTS

(1) No Obviousness-type Double Patenting is Present

In the final Office Action, Claims 30, 32-39, 41-51, and 53-65 were rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 1-24 of U.S. Patent No. 6,780,405 (hereinafter "the '405 patent"). Specifically, the Examiner contended that although the claims are not identical, they are not patentably distinct, stating:

> "the allowed species of method of inducing an immunoprotective immune response in a vertebrate anticipates the instantly claimed invention of inducing any type of immune response in an animal, wherein the composition administered in the instant Application comprises a bacteria that may or may not be attenuated, but the allowed species of microorganism must be attenuated, the viability system of the instant Application may be controlled by any number o[f] regulate[]able control sequences, but the allowed method administers a species which requires specific regulatory sequences." (Office Action dated January 12, 2005, page 4.)

No issue of obviousness-type double patenting is present considering the claims on appeal and the claims of the '405 patent. Obviousness-type double patenting is a doctrine aimed at preventing an extension of the patent right by seeking additional patents on subject matter that differs insignificantly from a patent already obtained. The doctrine requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent. *In re Braat*, 937 F.2d 589, 592, 19 U.S.P.Q.2D (BNA) 1289, 1291-92 (Fed. Cir. 1991). The purpose of the doctrine is to prevent an unjustified extension of the term of the patent right to exclude by allowing a second patent claiming an obvious variant of the same invention to issue to the same owner. *In re Goodman*, 11 F.3d 1046, 1052, 29 U.S.P.Q.2D (BNA) 2010, 2015 (Fed. Cir. 1993).

The judge-made law of obviousness-type double patenting was developed to cover the situation where patents are not citable as a reference against each other and therefore can not be examined for compliance with the rule that only one patent is available per invention. Double patenting thus is applied when neither patent is prior art against the other. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1278-81, 23 U.S.P.Q.2D (BNA) 1839, 1843-46 (Fed. Cir. 1992) (summarizing the criteria for obviousness-type double patenting). As the court explained in *In re Boylan*,

> "it must always be carefully observed that the appellant's patent is not 'prior art' under either section 102 or section 103 of the 1952 Patent Act." 55 C.C.P.A. 1041, 392 F.2d 1017, 1018 n.1, 157 U.S.P.Q. (BNA) 370, 371 n.1 (CCPA 1968).

Analysis

An obviousness-type double patenting analysis entails two steps. First, the Examiner must construe the claims in the earlier patent and the claims in the later patent and determine the differences. MPEP §804; *Georgia-Pacific Corp. v. United States Gypsum Co.*, 195 F.3d 1322, 1326, 52 U.S.P.Q.2d (BNA) 1590, 1593 (Fed. Cir. 1999). Second, the Examiner must determine whether the differences in subject matter between the two claims render the claims patentably distinct. MPEP §804; *Id.* at 1327, 52 U.S.P.Q.2D (BNA) at 1595.

Since the doctrine of double patenting seeks to avoid unjustly extending patent rights at the expense of the public, the focus of any double patenting analysis necessarily is on the claims in the multiple patents or patent applications involved in the analysis. MPEP §804.

Appellants note the Examiner's comments regarding the comparison of the pending method claims with issued method Claim 24 of the '405 patent rather than issued composition Claim 1. However, Appellants point out that issued method Claim 24 of the '405 patent merely states a method of inducing immunoprotection via administration of the composition of Claim 1 (via Claim 19, which depends from Claim 5, which ultimately depends from Claim 1):

"24. A method of inducing immunoprotection in a vertebrate comprising administering the vaccine of claim 19 to the vertebrate."

"19. A vaccine for immunization of a vertebrate, the vaccine comprising the microorganism of claim 5."

"5. The microorganism of claim 1, wherein (a) the vector is a plasmid; (b) the desired gene product is an antigen and (c) the microorganism is a Salmonella sp."

"1. A microorganism comprising a regulated antigen delivery system (RADS), wherein the RADS comprises (a) a vector comprising (1) a gene encoding a desired product inserted into a site for insertion of a gene encoding a desired gene product, wherein the gene encoding the desired gene product is operably linked to a second control sequence; (2) a first origin of replication (ori) conferring vector replication using DNA polymerase III; and (3) a second ori conferring vector replication using DNA polymerase I, wherein the second ori is operably linked to a first control sequence repressible by a first repressor, and wherein the runaway vector does not comprise a phage lysis gene; and (b) a gene encoding a first repressor operably linked to a first activatible control sequence.

Accordingly, Appellants submit that the obviousness-type double patenting rejection is ultimately a comparison of the two vaccine microorganisms and therefore Appellants comparison of the subject matter of the claims (reproduced below) is appropriate and probative of the issue at hand.

A comparison of the independent claims of the present invention and US Patent No. 6,780,405 is set forth below:

Appealed Claim 30	**Main Claim of the '405 Patent**
30. A method for inducing an immune response in a warm-blooded animal comprising administering to the animal a composition comprising a bacterial cell, wherein	1. A microorganism comprising a regulated antigen delivery system (RADS), wherein the RADS comprises
(a) the bacterial cell comprises an expression gene that encodes an antigen, and an Environmentally Limited Viability System,	(a) a vector comprising
(b) the antigen is introduced into the animal,	(1) a gene encoding a desired product inserted into a site for insertion of a gene encoding a desired gene product, wherein the gene encoding the desired gene product is operably linked to a second control sequence;
(c) **the bacterial cell is viable when in the animal and non-viable when outside of the animal**, and	(2) a first origin of replication (ori) conferring vector replication using DNA polymerase III; and
(d) the Environmentally Limited Viability	(3) a second ori conferring vector replication

System comprises **an essential gene that is under the control of an environmentally regulatable control sequence**, wherein	using DNA polymerase I,
(i) expression of the essential gene in the cell is essential to the viability of the cell,	wherein the second ori is operably linked to a first control sequence repressible by a first repressor, and wherein the runaway vector does not comprise a phage lysis gene; and
(ii) **the essential gene is expressed when the cell is in the animal and is not expressed when the cell is outside of the animal,**	(b) a gene encoding a first repressor operably linked to a first activatible control sequence.
(iii) the essential gene is essential for metabolism, growth, cell wall integrity or cell membrane integrity of the bacterial cell, and	
(iv) the essential gene is a copy of a native chromosomal gene wherein the chromosomal copy of said native gene is inoperable.	

In the foregoing table, bold type emphasizes particularly patentably distinct features and substantial differences in the subject matter of the appeal Claim 30 and the main Claim of the '405 patent.

It is clear that the claims of the present application are quite distinguishable from the claims of the '405 patent and are patentably distinct. The present invention and claims are directed to environmentally limited viability systems (ELVS) for microbes based on differences in environmental conditions, i.e., permissive and non-permissive environments. Viability of the microorganisms is limited to the permissive environment by making one or more essential genes of the microorganism expressible only in the permissive environment, and/or making one or more lethal genes expressible only in the non-permissive environment. One of the objects of the present invention was to develop an alternative biological containment system specifically suited for vaccine use, *i.e.*, an alternative to biological containment systems in which a suicide gene, that is, a gene that *actively* kills the microorganism, is the primary containment option. The complexity and high selective pressure to develop an inactivating mutation in the killing gene (or its regulators) make "lethal gene only" containment systems impractical, particularly for the vaccine field. Appellants have designed a novel alternative that avoids the problems associated with the actively lethal systems by providing a containment system that regulates an essential gene, *i.e.*, a gene or gene product that is essential for metabolism, growth, cell wall integrity, or cell membrane integrity. By use of the regulation methods described in Appellants' specification, the essential gene can be regulated to be only transcribed/expressed in a permissive environment.

In contrast, the '405 patent **claims** are directed to regulated antigen delivery systems (RADS) utilizing microorganisms containing a runaway vector containing two origins of replication (one low

copy, one high copy) and at least one chromosome-encoded regulated repressor, in which the copy number of the runaway vector increases in response to reduced levels of the repressor responsible for repression of the high copy number *ori* of the vector. In operation, the RAD system allows for the foreign gene to be stably maintained on the plasmid at a low copy number, which is optimal during growing conditions (such as in a fermenter). Under desired conditions such as upon inoculation, however, the vector is activated into a "runaway" state by regulated de-repression of the high copy number *ori* and de-repression of foreign gene expression.

The object of the '405 patent is to design a system that produces (*i.e.*, by runaway expression) and releases large amounts of antigen at a desired time, e.g., after inoculation. The claims of the '405 patent recite the particular elements necessary to bring about high levels of antigen production at the appropriate time (but not before).

It is clear that the claims on appeal are readily distinguishable and not obvious variants over the claims of the '405 patent. The present claims, *inter alia*, call for:

- a gene essential for metabolism, growth, cell wall integrity or cell membrane integrity of the bacterial that is under the control of an environmentally regulatable control sequence; and
- the essential gene is expressed when the cell is in the vaccinated animal and is not expressed when the cell is outside of the animal, which renders the bacterial cell viable when in the animal and non-viable when shed by the animal

The **claims** of the '405 patent call for:

- a regulated antigen delivery systems utilizing microorganisms containing a dual-*ori* (one low copy, one high copy) runaway vector and at least one chromosome-encoded regulated repressor

Appellants note that the Examiner has focused on Appellants' specification to support for her contention that the appealed claims are obvious variants of the claims of the '405 patent, *see, e.g.*, pages 2-3 of the Advisory Action. However, once again Appellants point out that the focus of any double patenting analysis necessarily is on the claims in the patent and patent application involved in the analysis. As the CAFC has stated regarding obviousness-type double patenting:

> "Under that facet of the doctrine of double panting, we must direct our inquiry to whether the claimed invention in the application for the second patent would have been obvious from **the subject matter *of the claims* in the first patent**, in light of the prior art." *In re Longi,* 225 USPQ 645, 648 (Fed. Cir. 1985) (citing *Carman Industries Inc. v. Wahl,* 220 USPQ 481, 487 (Fed. Cir. 1983)) (emphasis added).
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> ***
>
> "When considering whether the invention defined in a claim of an application [would have been] an obvious variation of the invention defined in the claim of a patent, **the disclosure of the patent may not**

> **be used as prior art**." *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 U.S.P.Q.2d 1839, 1846 (Fed. Cir. 1992); see, also, MPEP §804(II)(B)(1).

Appellants note that the Examiner's primary basis for the obviousness-type double patenting rejection concerns a discussion in the '405 ***specification*** regarding the Regulated Antigen Delivery system having an inherent containment system. Appellants note the Examiner's comments:

> "'405 at col. 23, lines 21-38 and col. 24, lines 32-35 defines the RADS to comprise ELVS components and '405, allowed claims 21-22 are so defined:" (Advisory Action, page 2.)

However, Claims 21 and 22 merely recite details of the runaway expression plasmid's two origins of replication and the control sequences used in the regulated antigen delivery system. There is no reference to a containment system or ELVS in these claims. This is further emphasized by the quotation of the RADS specification which the Examiner claims is necessary to interpret Claims 21-22:

> "In addition, the RADS with a [runaway vector] comprising a transfer vector ***can be*** designed as an ELVS that lysis [sic, lyses] due to regulated lysis genes inserted into the chromosome. Such expression of lysis genes would exhibit delayed expression such that lysis would only occur after the vertebrate cells with the transfer vector had entered a eukaryotic cell and conferred runaway vector replication. See also Example 6, which describes novel transfer vector adaptations to the RADS. When properly designed, the ELVS system is fully compatible with the RADS system and may share control elements." (Column 23, lines 27-36 of US Patent No. 6,780,405, emphasis added.)

Again, Appellants note that this is an improper reference to the specification – **there is no reference to a containment system or regulated lysis genes in the claims of the '405 patent requiring reference to the specification for definition or even support**. Appellants emphasize that the **disclosure of the patent may not be used as prior art** and that the patent is **not prior art** against the present application. Once again, since the doctrine of double patenting seeks to avoid unjustly extending claimed patent rights at the expense of the public, the focus of any double patenting analysis necessarily is on the claims in the multiple patents or patent applications involved in the analysis. MPEP §804. The public will not be subjected to two patents covering essentially the same subject matter if the appeal claims are allowed.

Moreover, Appellants note that the "containment system" cursorily mentioned in the '405 specification (and absent in the '405 claims) functions through *an entirely different* mechanism than claimed herein. In the RADS system of the '405 patent, a gene encoding a desired gene product is placed

on a runaway vector which, under repressed conditions, does not express foreign gene product and is maintained at low copy number. When the repression of the second *ori* and the second repressible control sequence is removed, the runaway vector is now "under derepressed runaway conditions", and both the copy number of the vector and the expression of the desired (foreign) gene product increase dramatically. The high copy number replication of the vector and the high expression of a foreign gene eventually overwhelm the host microorganism: the energy requirements of high copy replication and high foreign gene expression drain the cell and interfere with production of native proteins required to maintain the viability of the cell. The cell growth rate lowers under the burden of replicating the runaway vector and overexpressing the foreign gene product, and the host cell becomes vulnerable to other factors (such as immune attack). This is confirmed by the specification of the '405 patent:

> "Under derepressed runaway conditions, the RADS microorganism is highly impaired due to extremely high plasmid replication activity coupled with extremely high foreign gene product production. Because of its impaired state, the derepressed RADS microorganism cannot generally survive for extended periods. The RADS therefore features an inherent containment system, in which the RADS microorganism cannot survive when not exposed to the repressor gene-activating stimulus, **even in the absence of derepressible plasmid-derived phage lysis genes in the environmentally limited viability system (ELVS)** as disclosed in WO96/40917." (Column 6, lines 22-33 of US Patent No. 6,780,405, emphasis added.)

This indirect containment feature is, however, secondary to the technical advantage of having high foreign gene product expression occur at the most desirable point.

Accordingly, even if a containment system was recited in the '405 patent claims, which it is not, Appellants point out that the claims would *still be* patentably distinct because the *indirect* containment system described in the '405 specification (energy limitation) is wholly unrelated to the *direct* containment system of the present ELVS claims, wherein expression of a gene essential to the viability of the cell is ceased and, optionally, an actively lethal gene is expressed, when the microorganism is outside the host mammal.

The only similarity between the two sets of claims is that they both contemplate utilizing environmentally regulatable control sequences, for example, *araC*P_{BAD}. However, the present claims contemplate use of such sequences to control the expression of a gene essential to the viability of the cell, thus creating an environmentally limited viability. In contrast, the claims of the '405 patent contemplate the use of such control sequences for controlling the expression of repressors, which in turn control the replication of the dual-*ori* runaway expression plasmid, which in turn drives expression of the foreign antigen.

The Examiner attempts to link this one common element between the two cases:

> "The microorganism of allowed claim 7 of the '405 is defined to comprise not only the RAD/RAV system, but also to comprise the ELVS system and is administered in the method of allowed claim 24. Therefore, the allowed claim 24 of the '405 is directed to a species which utilizes a specific environmentally regulatable control sequence, specifically araCPbad. The allowed species anticipates the instantly claimed genus of method now claimed." (Office Action dated November 8, 2006, page 5.)

Appellants note the claims of the '405 do not "anticipate" the present invention as suggested. The claims of the '405 patent do not cover an ELVS wherein viability of the cell is controlled by the environmentally controlled expression of a gene essential for metabolism, growth, cell wall integrity or cell membrane integrity of the bacterial cell. Nor is an "anticipation" analysis applicable in an obvious-type double patenting rejection. Moreover, this statement is *factually* incorrect. Claim 7 of the '405 patent actually recites:

> 7. The microorganism of Claim 5, wherein the first activatable control sequence is *araC*P_{BAD}.

Following the thread of dependency to Claim 1 of the '405 patent reveals that said "first activatible control sequence" is found in step (b), which recites:

> "(b) a gene encoding **a first repressor** operably linked to a *first activatible control sequence*."

In the '405 patent antigen delivery system, the first repressor functions to repress the second origin of replication on the runaway expression plasmid, not, as the Examiner states, to function as the ELV system recited in the present claims. There is no regulated expression of an essential gene ELV system in the claims of the '405 patent.

Accordingly, since the methods of the present invention contain components and advantages not taught or suggested by the claims of the '405 patent, the present claims are NOT obvious variants of the prior patented claims and Appellants respectfully request reversal of the rejection under the judicially created doctrine of obviousness-type double patenting.

(2) Claims 61-64 are enabled under 35 U.S.C. §112, first paragraph

Claims 61-64 are rejected under 35 U.S.C. §112, first paragraph, as non-enabled, i.e., containing subject matter which is not described in the specification in such a way as to enable one skilled in the art

to make and use the invention. Specifically, the Examiner objects to Claim 61, which further specifies plasmid pMEG-104, as not being supported by the specification in sufficient detail so as to be reproducible by a person skilled in the art.

In their Response after final rejection mailed April 14, 2006, Appellants attempted to cancel Claims 61-64 to obviate this rejection. However, the Examiner, by refusing to enter Appellants' amendment after final, has maintained this issue on appeal. Accordingly, to be fully responsive, Appellants address the issue below.

The enablement requirements of 35 U.S.C. §112, first paragraph, may be satisfied by a deposit of the plasmid vector in accordance with 37 C.F.R. §1.802. As noted by the Examiner in the Office Action dated January 12, 2005:

> "An affidavit or declaration by Applicants, or a statement by an attorney of record stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of a patent, would satisfy the deposit requirements." (Office Action dated January 12, 2005, page 9.)

Accordingly, to be fully response to the Office Action, Appellants submit herewith (*see,* Exhibit A) a deposit statement in accordance with 37 C.F.R. §1.802. Appellants reiterate that such a receipt and statement is being presented at such a late stage of the proceedings because of the Examiner's failure to allow Appellants to cancel the offending claims from the claim set to eliminate the issue from appeal.

Appellants include herewith a copy of the receipt evidencing deposit of the microorganism designated MGN-417, which harbors plasmid pMEG-104, under the terms of the Budapest Treaty, with the American Type Culture Collection (ATCC), Rockville, MD 20852.

Additionally, given the opportunity, Appellants will amended the specification as requested to include the (ATCC) reference number (ATCC# 69836), the date of deposit (June, 1995), and the complete name and full street address of the international depository.

The indication that a deposit has been made under the conditions prescribed by the Budapest Treaty satisfies all conditions of the deposit regulations except the requirement that all restriction on access be removed upon grant of a patent. MPEP §2410.01. Accordingly, pursuant to 37 C.F.R. §1.808, Appellants, through their undersigned attorney of record, declare that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository.

In the event that the deposit records are not accepted, to be fully responsive, Appellants address the issue below.

The Person Skilled in the Art

Critical to the understanding of the invention and the proper consideration of this appeal is a recognition of the qualities of the "person skilled in the art to which [the invention] pertains", who within the meaning of 35 U.S.C. §112, first paragraph, is either enabled by the specification to practice the claims, or is not. The present specification is addressed to a person having expertise in the field of microbiology, with an understanding of immunology, cell biology, and molecular biology, who is knowledgeable of the techniques available at the time of the present invention for collecting, purifying, and recombinantly altering plasmids and cells.

The Standards for Enablement Under 35 U.S.C. §112, First Paragraph

It is incumbent on the Examiner in rejecting claims under the first paragraph of 35 U.S.C. §112 to establish a *prima facie* case of lack of enablement. *In re Strahilevitz*, 668 F.2d 1229, 1232; 212 USPQ 561, 563 (CCPA 1982). In determining whether or not a disclosure is enabling, it has been consistently held that the enablement requirement of 35 U.S.C. §112, first paragraph, requires nothing more than objective enablement, *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971); and in meeting the enablement requirement, the applicant's specification need not teach, and preferably omits, that which is well-known in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

How the enabling teaching is set forth, whether by the use of illustrative examples or by broad descriptive terminology, is of no importance, since the specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of 35 U.S.C. §112 unless there is a reason to doubt the objective truth of the statements relied upon for enabling support. *In re Marzocchi*, 439 F.2d at 223, 169 USPQ at 369 (CCPA 1971). A specification is considered to be enabling if a person skilled in the art could "make and use" the claimed invention without "undue experimentation". *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

"Whether making and using an invention would have required undue experimentation, and thus, whether a disclosure is enabling under 35 U.S.C. § 112 ... is a legal conclusion based upon underlying factual inquiries." *Johns Hopkins University v. CellPro, Inc.*, 152 F.3d 1342, 1354, 47 USPQ2d 1705, 1713 (Fed. Cir. 1998). Factors to be considered in determining whether a disclosure would require "undue" experimentation include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of the routineer in the art, (7) the predictability or lack thereof in the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731,

737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Appellants submit that the reproduction of plasmid pMEG-104, particularly in view of the teachings of Appellants' specification, is within the purview of the skilled practitioner. Appellants note that plasmid pMEG-104 is diagrammed in detail in Figure 4 of the application. Additionally, the skilled practitioner is given detailed steps on how to arrive at pMEG-104 from publicly disclosed starting materials and methods known in the art. *See, e.g.*, Table 2 on pages 28-29 of the specification. Moreover, the skilled practitioner is given further detailed instruction on how to produce pMEG-104 in Example 1 on pages 46-49 of the application:

> The methods used to produce the components of the ELVS illustrated in FIG. 4 employed standard molecular cloning techniques. The ELVS depicted in FIG. 4 consists of two main components. The first component is the ELVS vector which combines the application of a temperature regulated essential gene, *asd*, with the temperature regulated lethal genes, *lys13* and *lys19*, oriented in a manner to provide additional regulation by antisense RNA for both essential and lethal genes. The second component is the ELVS host required to maintain the ELVS vector, which for the *S. typhimurium* examples used the host MGN-392, possessing a defined asd deletion with a thermosensitive *cI857* and *c2* repressor cartridge insert.
>
> The ELVS expression vector pMEG-104, was constructed by the assembly of six individual components consisting of 1) the *S. typhimurium asd* gene, 2) the bacteriophage lambda promoter left to drive the *asd* gene, 3) the bacteriophage P22 lysis genes *lys13* and *lys19*, 4) the bacteriophage P22 promoter right to drive the lysis genes, 5) the *trpA* terminator to prevent transcription from external promoters, and 6) the expression vector core obtained from pYA810 (Galan et al. (1990)), consisting of the p15A origin of replication, the strong *trc* promoter, multiple cloning site used in existing Asd^+ vectors, and the ribosomal transcription terminators 5S T1 T2 to prevent transcriptional interference from the *trc* promoter. Many of these vector components were obtained by PCR amplification as described below, followed by modification of the DNA ends with either restriction enzymes or polymerases to allow assembly of the intermediate constructs. The *asd* gene of *S. typhimurium* was obtained by PCR amplification of the region between nucleotides 314 to 1421 of the S. typhimurium asd sequence as found on pYA292 (Galan et al. (1990)). This *asd* PCR product, a 1115 bp fragment with one end blunt and the other having a BglII overhang and lacking the promoter and Shine-Dalgarno regions of the *asd* gene, was cloned into the lambda promoter left vector, pMEG-076, in an orientation to produce an *asd* gene driven by the bacteriophage lambda promoter left. The result is plasmid pMEG-086.
>
> The promoter left of bacteriophage lambda present on pMEG-076 was obtained by PCR amplification of the region between nucleotides 5 to

160 of the promoter left sequence (Giladi et al., J. Mol. Biol. 231:109-121 (1990)). The resulting 155 bp fragment, with a blunt end and a *Bam*HI end, was cloned into the *Sma*I to *Bam*HI sites of the promoter probe cloning vector pKK232-8 (Brosius, J. Gene 27:151 (1984)), resulting in vector pMEG-086. In this vector, the *asd* gene is driven by the lambda promoter left.

The 1277 bp *Eco*RI to *Xba*I fragment of pMEG-086 containing the λP_L driven *asd* gene was then sub-cloned into the *Pvu*II to *Xba*I sites of the bacteriophage P22 *PR lys13 lys19* vector pMEG-089 using a synthetic *trpA* terminator, containing an internal *Bgl*II site and an *Eco*RI end, to produce pMEG-097. The relative orientation of the transcriptional elements for *asd* and *lys13 lys19* in pMEG-097 results in convergent transcription which produces antisense RNA for the *asd* and *lys* genes at differential temperatures.

The bacteriophage P22 lysis genes used in the construction of pMEG-097 were obtained by PCR amplification of nucleotides 62 to 850 of the P22 lysis gene region (Rennell et al., Virology 142:280-289 (1985)). The resulting 797 bp fragment, with an introduced Shine-Dalgarno site, a 5' blunt end, and a *Pst*I site designed into the 3' end, was cloned into the *Eco*RV to *Pst*I sites of the low copy-number vector pWKS30 (Kushner, S. Gene 100:195-199 (1990)). The resulting vector, pMEG-078, has the *lys13* and *lys19* genes under control of the *lac* promoter. The lysis genes were then sub-cloned as a 1060 bp *Sal*I to *Pvu*II fragment from pMEG-078 into the SalI to PvuII sites of the P22 promoter right expression vector, pMEG-072. In the resulting vector, pMEG-089, the bacteriophage P22 lysis genes *lys13 lys19* are driven by the P22 promoter right. The bacteriophage P22 promoter right in pMEG-072 was obtained by PCR amplification of the region between nucleotides 23 and 138 of the P22 promoter right sequence (Poteete et al., J. Mol. Biol. 137:81-91 (1980)). The resulting 125 bp *Bam*HI to *Sal*I fragment was cloned into the *Bam*HI to *Sal*I sites of the promoter probe vector pKK232-8 (Brosius, J., Gene 27:151 (1984)) to produce pMEG-072.

The *asd lys13 lys19* cartridge present in pMEG-097 contains both the essential and lethal genes separated by a portion of the multiple cloning site, including a *Bam*HI site from previous manipulations. This region was deleted from pMEG-097 as a 28 bp *Pst*I-*Xba*I fragment, and the remaining vector was treated with T4 DNA polymerase prior to religating. This resulted in vector pMEG-098, containing the *asd lys13 lys19* cartridge. The *asd lys13 lys19* cartridge was then transferred to the expression vector core of pMEG-090 by digesting pMEG-090 with BglII and inserting the 2.26 kb BamHI to BglII fragment of pMEG-098 containing the *asd lys13 lys19* cartridge. This produced pMEG-100, shown in FIG. 5.

Vector pMEG-090 was derived from pYA810 by performing a partial *Bgl*II digest of pYA810; isolating the 1.6 kb fragment of pYA810 containing the p15A origin of replication, the *trc* promoter, and the multiple cloning site with the transcriptional terminator; and ligating the

> fragment to the 1.3 kb *Bam*HI kanamycin resistance element of pUC-4K (Christie G. E., et al., Proc. Natl. Acad. Sci. USA 78:4180 (1981)).
>
> In pMEG-100, the essential and lethal genes are flanked by two different transcriptional terminators, the first is the *trpA* terminator (Christie et al., Proc. Natl. Acad. Sci. USA 78:4180 (1981)) and the other is the ribosomal 5S terminator repeat cartridge used in the previously described Asd^+ balanced-lethal vectors pYA248 and pYA292 (EP 89900028.5). Vector pMEG-100 also contains the lower copy-number DNA polymerase I-dependent p15A origin of replication and the strong *trc* promoter derived from pYA810 and used in the pYA292 Asd^+ vector described in EP 89900028.5. The kanamycin resistance element of pMEG-100 was then removed by a partial *Sal*I digest to produce pMEG-104, the ELVS vector shown in FIG. 4.

Accordingly, Appellants submit that persons skilled in the art, having read and understood the teachings of Appellants' specification, could certainly reproduce plasmid pMEG-104 from available starting materials, given the foregoing directions quoted from the specification . The claims are fully enabled; accordingly, Appellants request reversal of the rejection of Claims 61-64 under 35 U.S.C. §112, first paragraph.

CONCLUSION

In view of the foregoing remarks Appellants submit that the present claims are clearly patentably distinct from the allowed claims of US Patent No. 6,780,405 and that in making the obviousness-type double patenting rejection, the Examiner is inappropriately relying on the '405 specification for the rejection when it is apparent that the claims of the '405 patent on their face do not recite an environmentally limited viability system.

Additionally, Appellants submit that the Claims 61-64, which specify plasmid pMEG-104 are fully enabled and that persons skilled in the art, having read the detailed teachings of Appellants specification, would be able to make and use the invention as recited in Claims 61-64 without hindrance or undue experimentation.

For the reasons set forth herein, the final rejection of Claims 30, 32-39, 41-51, and 53-65 under the judicially-created doctrine of obviousness-type double patenting as well as the rejection of Claims 61-64 as non-enabled under 35 U.S.C. §112, first paragraph, are believed to be error and should be reversed by this Board.

Respectfully submitted,

Leon R. Yankwich, Reg. No. 30,237
Michael R. Wesolowski, Reg. No. 50,944
Attorneys for Appellants
YANKWICH & ASSOCIATES, P.C.
201 Broadway
Cambridge, MA 02139
tel. (617) 374-3700

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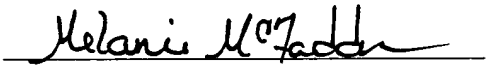

Melanie McFadden

COMPLETE LISTING OF ALL CLAIMS ON APPEAL, WITH STATUS IDENTIFIERS

1-29. (cancelled)

30. (previously presented, appealed) A method for inducing an immune response in a warm-blooded animal comprising administering to the animal a composition comprising a bacterial cell, wherein

(a) the bacterial cell comprises an expression gene that encodes an antigen, and an Environmentally Limited Viability System,

(b) the antigen is introduced into the animal,

(c) the bacterial cell is viable when in the animal and non-viable when outside of the animal, and

(d) the Environmentally Limited Viability System comprises an essential gene that is under the control of an environmentally regulatable control sequence, wherein

(i) expression of the essential gene in the cell is essential to the viability of the cell,

(ii) the essential gene is expressed when the cell is in the animal and is not expressed when the cell is outside of the animal,

(iii) the essential gene is essential for metabolism, growth, cell wall integrity or cell membrane integrity of the bacterial cell, and

(iv) the essential gene is a copy of a native chromosomal gene wherein the chromosomal copy of said native gene is inoperable.

31. (cancelled)

32. (previously presented, appealed) The method of claim 30 wherein the antigen is selected from the group consisting of bacterial antigens, viral antigens, plant antigens, fungal antigens, insect antigens, and non-insect animal antigens.

33. (previously presented, appealed) The method of claim 30, wherein the composition is administered to mucousal surfaces of the animal.

34. (cancelled)

35. (previously presented, appealed) The method of claim 39, wherein the system further comprises a replication gene carried on a chromosome of the cell, the expression of which is required for replication

of the vector, wherein the replication gene is expressed when the cell is in the animal and not expressed when the cell is outside the animal, wherein the cell is a member of the *Enterobacteriaceae*.

36. (previously presented, appealed) The method of claim 30, wherein the bacterial cell is a member of the *Enterobacteriaceae*.

37. (previously presented, appealed) The method of claim 36, wherein the bacterial cell is an avirulent *Salmonella*.

38. (previously presented, appealed) The method of claim 37, wherein the avirulent *Salmonella* is an avirulent derivative of a pathogenic *Salmonella* that attaches to, invades and persists in the gut-associated lymphoid tissue or bronchial-associated lymphoid tissue.

39. (previously presented, appealed) The method of claim 30, wherein the system further comprises a lethal gene, wherein the expression of the lethal gene is lethal to the cell and the lethal gene is expressed when the cell is outside the animal but not when the cell is in the animal.

40. (cancelled)

41. (previously presented, appealed) The method of claim 30, wherein the essential gene encodes an enzyme which catalyzes the biosynthesis of the cell wall and its precursors.

42. (previously presented, appealed) The method of claim 41, wherein the essential gene encodes an enzyme which catalyzes a step in the biosynthesis of diaminopimelic acid (DAP).

43. (previously presented, appealed) The method of claim 42, wherein the essential gene is the gene encoding β-aspartate semialdehyde dehydrogenase (*asd*).

44. (previously presented, appealed) The method of claim 30, wherein the essential gene is selected from the group consisting of

genes encoding enzymes which catalyze steps in the biosynthesis of diaminopimelic acid (DAP) *dap*A, *dapB*, *dapC*, *dapD*, and *dapE*, the gene encoding alanine racemase (*dal*), the gene encoding D-alanyl D-alanine ligase (*ddl*), genes involved in fatty acid biosynthesis (*fab*),fatty acid degradation (*fad*),phospholipid synthesis (*pls*), a gene encoding a modification methylase, a gene encoding a DNA ligase, a gene encoding a DNA gyrase, and a gene encoding a phospholipase.

45. (previously presented, appealed) The method of claim 39, wherein the lethal gene is selected from the group consisting of a member of the *gef* family, a plasmid maintenance gene, a gene encoding a nuclease, a gene encoding a phospholipase, a gene encoding an endolysin, a gene encoding a holin, and a gene encoding the tRNA with a wrong codon.

46. (previously presented, appealed) The method of claim 45 wherein the lethal gene is the combination of bacteriophage P22 lysis genes 13 and 19.

47. (previously presented, appealed) The method of claim 35, wherein the replication gene is the gene encoding deoxyribonucleic acid polymerase I, (*polA*).

48. (previously presented, appealed) The method of claim 39, wherein the expression of the essential gene or the lethal gene is regulated by a trans regulatory element.

49. (previously presented, appealed) The method of claim 48, wherein the trans regulatory element is selected from the group consisting of a repressor, an antisense RNA, and an RNA polymerase.

50. (previously presented, appealed) The method of claim 39, wherein expression of the essential gene or the lethal gene is regulated by using promoters or regulatory elements that are regulated by temperature, or by other regulatory systems adapted to function in a temperature-dependent manner.

51. (previously presented, appealed) The method of claim 50, wherein the essential gene is regulated by being operatively linked to either

(a) a *virB* promoter, wherein the bacterial cell further comprises a *virF* gene and promoter; or

(b) a *virF* positive activator in combination with a promoter of *yopH* gene or a *yadR* gene.

52. (cancelled)

53. (previously presented, appealed) The method of claim 51, wherein the essential gene is regulated by a bacteriophage lambda promoter left or right (λP_L or λP_R) promoter with a temperature sensitive bacteriophage lambda *cI857* repressor.

54. (previously presented, appealed) The method of claim 53, wherein the *cI857* repressor is operatively linked to a P*trc* promoter.

55. (previously presented, appealed) The method of claim 51, wherein expression of the lysis gene is regulated by a bacteriophage P22 P_R promoter operatively linked to a P22 *c2* gene, wherein the P22 *c2* gene is regulated by a P_L promoter, and wherein the cell further comprises a chromosomal *cI857* gene.

56. (previously presented, appealed) The method of claim 55, further comprising an essential gene operatively linked to a λP_L promoter.

57. (previously presented, appealed) The method of claim 56, wherein the *cI857* repressor is inserted into an inactive chromosomal gene, wherein the inactive chromosomal gene is an inactive essential gene.

58. (previously presented, appealed) The method of claim 57, wherein the microbial cell is an avirulent *Salmonella*.

59. (previously presented, appealed) The method of claim 58, wherein the avirulent *Salmonella* is an avirulent derivative of a pathogenic *Salmonella* that attaches to, invades and persists in the gut-associated lymphoid tissue or bronchial-associated lymphoid tissue.

60. (previously presented, appealed) The method of claim 59, wherein the avirulent *Salmonella* further comprises an inactive gene selected from the group consisting of *cya, crp, phoP, phoQ, ompR, galE, cdt, htrA*, and a gene with a mutation that imposes a requirement for an aromatic amino acid or a vitamin.

61. (previously presented, appealed) The method of claim 57, wherein the extrachromosomal vector comprises pMEG-104.

62. (previously presented, appealed) The method of claim 61, wherein the extrachromosomal vector further comprises an expression gene.

63. (previously presented, appealed) The method of claim 62, wherein the expression gene encodes an antigen.

64. (previously presented, appealed) The method of claim 63, wherein the antigen is selected from the group consisting of a bacterial antigen, a viral antigen, a mycotic antigen, a parasitic antigen, a gamete specific antigen, and a tumor antigen.

65. (previously presented, appealed) The method of claim 31, wherein the antigen is selected from a group consisting of a bacterial antigen, a viral antigen, a mycotic antigen, a parasitic antigen, a gamete specific antigen, and a tumor antigen.

EVIDENCE APPENDIX

1. A copy of the receipt evidencing deposit of the microorganism designated MGN-417, which harbors plasmid pMEG-104, under the terms of the Budapest Treaty, with the American Type Culture Collection (ATCC), Rockville, MD 20852. Attached evidence is not of record. Appellants request entry of the receipt pursuant to 37 C.F.R. § 41.33(c).

JUN 05 '95 11:38AM

Budapest Treaty Depositary

American Type Culture Collection

12301 Parklawn Drive, Rockville, MD 20852 USA, Telephone (301) 231-5520

TO DEPOSIT OR TO CONVERT A DEPOSIT TO MEET THE REQUIREMENTS OF BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

1. Name of deposit (e.g., microorganism, cell line, seed, plasmid, etc.). If cell line, please provide species:
   Salmonella typhimurium
2. Strain designation (i.e., number, symbols, etc). MGN-417 containing plasmid pMEG-[illegible]
   Δasd-17::cI857PRc2
3. Is this an original deposit under the Budapest Treaty? Yes
4. Is this a request for a conversion of a deposit already at the ATCC to meet the requirements of the Budapest Treaty? If so, please indicate ATCC designation. No
5. Is this deposit a mixture of microorganisms or cells? No
6. Provide details necessary to cultivate, test for viability and store deposit. If mixture, provide description of components and a method to check presence. Grow in Lennox broth @ 37°C; WILL NOT GROW AT 25°C. Store in 1% peptone+5% glycerol ° -70°C.
7. Provide an indication of the properties of the strain which are or may be dangerous to health or the environment.
   Derivative of S. typhimurium pathogenic for Mice
*8. Provide sufficient description so that ATCC may confirm deposit properties (e.g., Gram negative rod).
   Gram negative rod, agglutinates O-antigen group B antisera

   a. If deposit is a cell culture, is it being cultured in the presence of antibiotics? If so, please list the antibiotics.

   b. If deposit is hybridoma, what is the isotype of antibody produced?

*9. Is this strain zoopathogenic? phytopathogenic?

10. (MUST BE COMPLETED) Packaging Class I, II, III, IV [in accordance with U.S. Public Health Services Regulation 42 C.F.R. § 72.3 (a)-(f)]? Class II

11. Does this strain contain plasmids relevant to the patent process? Yes

    If so, what physical containment level is required (National Institutes of Health Guidelines Involving Recombinant DNA Molecules, i.e., P1, P2, P3 or P4 facility)? P2

*12. Isolated from? Laboratory derived strain

* The answers to these questions are recommended but not required.

ATCC USE ONLY

ATCC DESIGNATION _____ RECEIVED _____ V.T. RESULT & DATE _____

FEES: 30 years' storage $600. 30 years' notification $360. Viability testing $100 to $400 or quoted price, dependent upon necessary material and/or equipment. Expedite ATCC number $10. Return sample for approval (if not submitted frozen or freeze-dried) $30. Prepare additional samples of cells or hybridomas $500. Additional costs for return of samples outside U.S.A.
STORAGE: Cultures are stored for 30 years from date of deposit and for five years after the last request for a sample, as required under the rules of patent offices in most countries.

After a U.S. Patent [illegible] available to anyone who requests it, as allowed under U.S. law. Prior to issuance of a U.S. Patent, ATCC is to release a culture available as instructed by the depositor or relevant patent office. In addition to [illegible] under the Budapest Treaty and the European Patent Convention, do you wish the strain [illegible]

a. As of the date of [illegible] anyone who requests a culture? (If "yes", there are no restrictions on distribution from date of deposit or conversion to Budapest). No

b. To [illegible] patent offices in countries not signatory to the Budapest Treaty? If "yes", please state which [illegible] No

14. Do you wish ATCC to inform you of all requests for this strain? ($360 fee for 30-year informing). Yes

15. Would you like expedited notification of your ATCC number? ($10 fee). ATCC must observe viability first. Yes

Name of individual. Steven Tinge

Fax No. 314-776-3317 Telephone No. 314-776-1626

16. Payment by check, or credit card (MasterCard, VISA or American Express), must accompany the deposit unless prior arrangements for billing have been made and approved. If arrangements have been made to bill you for services, please indicate person who should receive invoice. Also, please include P.O. number.

Payment by check

Credit Card number (indicate MasterCard or VISA) Expiration Date

Type or print the name shown on credit card Signature

17. Name and address of your attorney of record. Patria Pabst, Arnall Golden & Gregory
2800 One Atlantic Center 1201 W. Peachtree, St., Atlanta, GA 30309

18. MUST BE COMPLETED. Owner of deposit. (Verify with your management who owns the deposit. The owner is usually a company or institute, and normally is not an individual.)
Washington University, St. Louis, MO

19. Additional comments.

I understand and agree that the deposit may not be withdrawn by me for a period specified in Rule 9.1 of the Budapest Treaty (at least 30 years after the date of deposit and 5 years after the date of the most recent request for the deposit), and that if a culture should die or be destroyed during the life of the patent, or the period of time so specified, it is my responsibility to replace it with a living culture of the same organism or cell. In the cases of viruses, cell cultures, plasmids, embryos, and seeds, it is my responsibility to supply a sufficient quantity for distribution for the period of time specified above.

Typed Name Roy Curtiss III Signature [signature] Date June 5, 1995

Address. Dept. of Biology, Campus Box 1137, One Brookings Drive
Washington University, St. Louis, MO 63130

THIS FORM MUST BE COMPLETED IN ENGLISH

ADDRESS SHIPMENTS AND FORM TO THE ATTENTION OF:

Ms. Annette L. Bade, Esq.
American Type Culture Collection
12301 Parklawn Drive
Rockville, MD 20852 U.S.A.

RELATED PROCEEDINGS APPENDIX

None.